AMENDMENTS TO THE SPECIFICATION

After the title, insert the following priority information:

-- Cross-Reference to Related Applications

This application is a national stage of International Patent Application No. PCT/EP2003/008052, filed July 4, 2003.

Background of the Invention --

On page 6, line 29, amend the heading according to the following:

-- ~~Statement~~ Summary of the Invention --

On page 10, on line 29, insert the following heading:

-- Brief Description of the Drawings --.

On page 37 and 39, replace the paragraph spanning page 37, lines 20-35 and page 39, lines 1-5 with the following paragraph:

-- Example 1 describes the synthesis of two exemplary Ω-sensitizers with two pheophorbide a or chlorin e6 moieties as active pair, respectively. As depicted in Figure 5 for pheophorbide a the Ω-sensitizer comprises a 20 mer TCS 20, 5'-TGC TAG GTT TCC TCC CTT TC-3' SEQ ID NO: 1, directed against the epidermal growth factor receptor (EGFR) mRNA. The TCS is directly flanked by two complementary arms 21 and 22 which form the stem duplex in the absence of the target. Two identical photosensitive moieties R are coupled via two different amino carbon spacers 23 and 24 to the 3' and the 5' terminus of the arms 21 and 22, respectively. Oligonucleotides were synthesized using an Applied Biosystems 394 DNA synthesizer (Perkin Elmer, Applied Biosystems Inc., Foster City, USA) and standard phosophoramidite chemistry. They were grown on a controlled pore glass support functionalized with an amine group attached via a ten atom linker (5'-DMT-T (C6 Amino)-Suc-CPG Biosearch Technologies, USA). The

amine group was protected with a trifluoroacetyl (TFA) protecting group. A TFA protected Aminohexyl Amidite (5' TFA-Amino C6 Modifier, Biosearch Technologies, USA) was used to produce a functional amine group on the 5' end of the oligonucleotide. The CPG support was treated with 28% ammonium hydroxide at 55°C for 8 hours following this and the ammonium hydroxide solution was evaporated in vacuo. --.

On page 39, replace the paragraph spanning lines 10-35 with the following paragraph:

-- The N-hydroxy succinimide(NHS). esters of both photosensitive moieties (pheophorbide a and chlorin e6 (Porphyrin Products, Logan, UT) were prepared by reacting 1.5 equivalents of dicyclohexylcarbodiimide and 1.5 ~~eqivalents~~ equivalents of NHS with 1 equivalent of chlorin e6 and ~~pheophrbide~~ pheophorbide a in dry dimethylsulfoxide in the dark for 24 hours at room temperature. The dry, crude oligonucleotide (20-250 nmols) was dissolved in sodium bicarbonate buffer (0.1 M, pH 9.3, 500μl) and 20 equivalents of the corresponding photosensitive moiety NHS ester (dissolved in 100 μl DMSO) were added in 10μl aliquots at 20 minute intervals to the mixture. After continuous stirring for 24 hours at room temperature, particulate matter was removed by spinning the mixture in a microcentrifuge for one minute at 10000 rpm. In order to remove unreacted photosensitive moiety, the supernatant was passed through a gel-exclusion column, equilibrated with 0.1 M triethylammonium acetate at pH 6.5. The resulting Ω-sensitizers were purified using a C-18 reverse phase column (Waters) HPLC utilizing a linear elution gradient of 20 to 70% of 0.1 M triethylammonium acetate in75% acetonitrile in 0.1 M triethylammonium acetate. HPLC was monitored at 280 nm and 665 nm. Fractions having peaks that at both wavelengths were collected, precipitated with ethanol and salt. After drying the Ω-sensitizers, 5'-(pheo a)-GCG ATG CTA GGT TTC CTC CCT TTG TCG C-(pheo a)-31 (SEQ ID NO: 2) and 5'-(chlorin)-GCG ATG CTA GGT TTC CTC CCT TTG TCG C-(chlorin)-3' (SEQ ID NO: 3), respectively, were ready to use. --.

On page 40, replace the paragraph spanning lines 1-6 with the following paragraph:

-- In a similar manner as described above control random Ω-sensitizers with the scrambled sequence 5'-GCG ACT GAC TGC CAA CTA TGA ACA TCG C-3' SEQ ID NO: 4 conjugated to pheophorbide a and chlorine e 6 were synthesized. The nucleic acid sequence 5'-CTG ACT GCC AAC TAT GAA CA-3' SEQ ID NO: 5 has been chosen because it has been shown to be GenBank negative for any known RNA match. --

On page 40, replace the paragraph spanning lines 10-32 with the following paragraph:

-- The selective photosensitizing action of the different Ω-sensitizers described in Example 1 was tested in vitro against sense oligonucleotides, and sense oligonucleotides having one and two base mismatches, respectively. For this purpose oligonucleotides with sequences 5'-CAA AGG GAG GAA ACC TAG CA-3' (sense) SEQ ID NO: 6, 5'-CAA AGG GAG GTA ACC TAG CA-3' (sense 1bp mismatch) SEQ ID NO: 7, and 5'-CAA AGG GAA GTA ACC TAG CA-3' (sense 2bp mismatch) SEQ ID NO: 8 were synthesized using standard automated phosphoramidite chemistry. Oligonucleotides were dissolved in 2ml of a solution containing 10mM Tris-HCl and 2mM $MgCl_2$ to give a final concentration of 0.8μM in a quartz cuvette. To this solution 1ml Dihydrorhodamine 123 (DHR123) (Molecular Probes, Eugene, USA) (40μM) dissolved in 10mM Tris-HCl was added. DHR123 is a non-fluorescent molecule that in the presence of oxygenating species undergoes oxygenation to give the fluorescent dye rhodamine123 having an absorption maximum at 507nm and a fluorescence maximum at 529nm. ~~1ml~~ One ml of Ω-sensitizer (800nM) containing solution was added and the final solution was stored in the dark at 37°C for 20 minutes. Then the solution was irradiated at 405±5nm with electromagnetic radiation from a filtered Hg-Arc lamp. The RH123 fluorescence intensity at 529nm was measured every 60 seconds using a Perkin Elmer spectrofluorometer (Model LS50B, Perkin Elmer, Rotkreuz, CH). --.

On pages 41-42, replace the paragraph spanning page 41, line 29 through page 42, line 20 with the following paragraph:

-- In order to test the possibility of using nano particles as the quenching moiety, oligonucleotides labeled with a photosensitive moiety at the 3' terminus, where labeled at the 5' terminus with amino modified gold nanoparticles. The mam gene sequence 5'-CGG ATG AAA CTC TGA GCA ATG TCT GCA GTT CTG TGA GCC AAA G-31 (GeneBank accession No. AF015224) SEQ ID NO: 9 was coupled to the complementary stem sequences CCA AGC and GCT TGG at its 5' and 3' termini, respectively. The sequence was constructed using fully automated DNA synthesis as described in Example 1. The 3' end contained an amino group, while the 5' end was equipped with a six carbon spacer thiol group protected by a trityl moiety (Glen Research, Sterling, Virginia) using standard methods. Following cleavage with28% ammonium hydroxide, oligonucleotides were washed and purified as described above. The 3' end photosensitive moiety labeled oligonucleotide was prepared and purified using the NHS ester of pheophorbide a as described in Example 1. Then the trityl protection group was removed by adding 0.15M silver nitrate solution to the labeled oligonucleotide for 1 hour. To this mixture 0.15M dithiothreitol (DTT) was added for 10 minutes. After spinning at 10000 rpm the supernatant was transferred to another tube. 400pmol of this oligonucleotide were then suspended in180μl of water and immediately reacted with6nmol of monomaleimido gold particles (Ø = 1. 4nm) (Nanoprobes) in aqueous 20mM NaH_2PO_4, 150mM NaCl, 1mM ethylenediamine tetraethyl acetate (EDTA) Buffer, pH 6.4, containing 10% isopropanol at 4°C for 24 hours. --.

On pages 42-43, replace the paragraph spanning page 42, line 22 through page 43, line 4 with the following paragraph:

-- To the solution containing the Ω-sensitizer, 5' (gold particle)-S-$(CH_2)_6$-**CCA AGC** CGG ATG AAA CTC. TGA GCA ATG TCT GCA GTT CTG TGA GCC AAA **GCT TGG**-(pheophorbide a)-3' SEQ ID NO: 10, target and one base pair mismatch oligonucleotides were added at different concentrations. After adding

appropriate quantities of DHR123 (see Example 1), the solutions were irradiated at 405nm with electromagnetic radiation doses of 10J/cm^2 and the fluorescence of rhodamine 123 was measured as described above as a function of the target concentration. Figure 9 shows the concentration dependence of Ω-sensitizer-induced photo-oxidation of DHR123 as measured by means of RH123 fluorescence at 529nm in the presence of a target sequence (squares) and in the presence of a one base pair mismatched oligonucleotide (circles). The fluorescence intensity in the presence of the target sequence reaches its maximum at a concentration of about 0.5μM of the target sequence, while no fluorescence is detectable at this concentration when the oligonucleotide is not complementary to the TCS. At only very high concentrations of the one base pair mismatched oligonucleotide can photodynamic action be observed. --.

On pages 43-44, replace the paragraph spanning page 43, line 8 through page 44, line 25 with the following paragraph:

-- In the case of breast cancer cell lines there is considerable evidence of altered integrin level expression in the tumorigenic situation in comparison with the native, parental background. AlphaV integrins are highly expressed and could have a prominent role in breast cancer metastasis to bone. Recently, cDNA sequences encoding the integrin alphaV from a variety of species were assessed using DNA Star and GCG molecular biology packages. From a number of sequences one 18 bp target region spanning nucleotide positions 40-57 in the human DNA was chosen. A modified Ω-sensitizer containing a quencher moiety on the 5' terminus and a photosensitizing moiety on the 3' terminus was produced. The corresponding alphaV 5543-ODN TCS sequence 5'-**GC*G AG*C*** **GGC*GGA AAA GC*C A*T*C *GTC*G C**-3' SEQ ID NO: 11 and the mismatch control sequence 5'-**GC*GAG*C*** **AAC*GAG AGA GC*C G*T*C* GTC*G C**-3' SEQ ID NO: 12 were synthesised as described previously (*represents phosphorthioate linkages). The 3' terminus was additionally modifier using a C6 thioether modifier as described above. All oligonucleotides were routinely synthesized as partial phosphorthioates under standard conditions. Oligonucleotides were synthesized

using an Applied Biosystem 394 DNA synthesizer (Perkin Elmer Applied Biosystems, Foster City, CA) and standard phosphoramitide chemistry. After coupling, phosphorthioate linkages were introduced by sulphorization using Beaucage reagent, followed by capping with acetic anhydride and N-methylimidazole. After cleavage from the solid support and final deprotection by treatment with concentrated ammonia, oligonucleotides were purified by polyacrylamide gel electrophoresis. Following purification chlorin e6 NHS ester was introduced as described in Example 1 at the 3' end. Then the trityl protection group was removed by adding 0.15M silver nitrate solution to the labeled oligonucleotide for 1 hour. To this mixture 0.15 M dithiothreitol (DTT) was added for 10 minutes. After spinning at 10000rpm the supernatant was transferred to another tube. ~~400pmol~~ Four hundred pmol of this oligonucleotide were then suspended in 180 µl of water and immediately reacted with QSY-7 maleimide (3.6mg) (Molecular Probes, Eugene, USA) and subsequently dissolved in DMF for 10 minutes at 65°C. Unreacted QSY-7 was removed with spin column chromatographic separation using a Sephadex G-25 spin column. After purification, Ω-sensitizers were incubated with target oligonucleotide (sequence 5'-CGA TGG CTT TTC CGC CGC-3' SEQ ID NO: 13) in a quartz cuvette and the intrinsic fluorescence of the photosensitive moiety ~~moiety~~ was followed at 664nm for 20 minutes. Figure 10 shows the fluorescence time profiles of the hybridization of the antisense and control Ω-sensitizer in the presence of the alphaV target sequence in the solution. Only slightly increasing fluorescence was observed with the random control Ω-sensitizer, while the antisense Ω-sensitizer developed within 25 minutes maximal fluorescence intensities due to hybridization to the target sequence. This indicates that treatment of cells expressing the alphaV integrin target cDNA will have maximal efficacy after about 30 minutes following incubation. --.

On page 46, replace the paragraphs spanning lines 27-33 with the following paragraphs:

-- a) 5' (chlorin e6)-GC*G A*T*G CTA GG*T* TTC CTC CCTT*T*G* T*C*GC-(chlorin e6) 3' SEQ ID NO: 14

b) 5' (chlorin e6)-GC*G A*CT GA*C TGC CA*A C*TA TG*A* ACA T*C*GC- (chlorin e6) 3' SEQ ID NO: 15

c) 5'-*T*G CTA GG*T* TTC CTC CCT T*T*G*-3' SEQ ID NO: 16 --.

Kindly add the attached Abstract as new page 53.